STUDY ON INFLUENCE OF FLAVONOIDS: IN DIABETES AND ITS COMPLICATIONS.

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1. Abstract of proposed work plan/ problem:

Diabetes is the most prevailing health concerns worldwide and their incidence is increasing at a high rate, resulting in enormous social costs. Diabetes Mellitus (DM) is a metabolic disorder characterized by the destruction of pancreatic cells or diminished insulin secretion. Obesity causes the development of metabolic disorders such as DM, hypertension, cardiovascular diseases, and inflammation-based pathologies.

Flavonoids are the secondary metabolites of plants and have 15-carbon skeleton structures containing two phenyl rings and a heterocyclic ring. More than 5000 naturally occurring flavonoids have been reported from various plants. Flavonoids have also been considered as health-promoting agents with proven in vitro and in vivo biological effects, which include nephroprotective, anti-arthritic, antidepressant, antibacterial, antioxidant, anticancer and antitumor, anti-ischemic, analgesic and anti-inflammatory. The therapeutic effects emerge from their influence on hormones via enzymes such as aromatase (a cytochromes P450 enzyme), mitogen-activated protein kinase (MAPK) such as p38, JNKs (Jun n-terminal kinases) and ERK1/2 (extracellular signal-regulated kinases 1/2), among other enzymes. Some flavonoids such as quercetin, resveratrol, EGCG have been found to possess many beneficial effects with advantages over modern drug treatments in DM. An effect of the potential health benefits of this flavonoids in treating DM, and show increased bioavailability.

2. Introduction:

DM is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia or raised blood sugar is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels (1). Recently WHO survey report the number of people with diabetes has risen sharply from 108 million in 1980 to 422 million in 2014. The global prevalence of DM among adults over 18 years of age has risen sharply from 4.7% in 1980 to 8.5% in 2014. DM prevalence has been rising more rapidly in middle- and low-income countries. In 2015 estimated 1.6 million deaths were directly caused by diabetes. Another 2.2 million deaths were attributable to high blood glucose in 2012 are almost half of all deaths attributable to high blood glucose occur before the age of 70 years. WHO projects that diabetes will be the seventh leading cause of death in 2030 (2). World Diabetes Day (WDD) is celebrated annually on November 14 (3).

►Etiology of DM:

Type 1 diabetes mellitus:

Type 1 diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency. Type 1 is usually characterized by the presence of anti–glutamic acid decarboxylase, islet cell or insulin antibodies which identify the autoimmune processes that lead to beta cell destruction. Eventually, all type1 diabetic patients will require insulin therapy to maintain normglycemia.

Type 2 diabetes mellitus:

The relative importance of defects in insulin secretion or in the peripheral action of the hormone in the occurrence of DM2 has been and will continue to be cause for discussion. DM2 comprises 80% to 90% of all cases of DM. Most individuals with Type 2 diabetes exhibit intra-abdominal (visceral) obesity, which is closely related to the presence of insulin resistance. In addition, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often are present in these individuals.

This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise (4).

►Pathophysiology of DM:

There is a direct link between hyperglycemia and physiological & behavioral responses. Whenever there is hyperglycemia, the brain recognizes it and sends a message through nerve impulses to pancreas and other organs to decrease its effect (5).

A. Type 1 DM:

Type 1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets. Several features characterize type 1 DM as an autoimmune disease (6).

Presence of immuno-competent and accessory cells in infiltrated pancreatic islets; Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA); Presence of islet cell specific autoantibodies; Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment; The involvement of monokines and TH1 cells producing interleukins in the disease process; Response to immunotherapy and; Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members. Approximately 85% of patients have circulating islet cell antibodies, and the majorities also have detectable anti-insulin antibodies before receiving insulin therapy. Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) within pancreatic B cells (7).

B. Type 2 DM:

In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 DM are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance (8).

►DM Complications:

Diabetes involves chronic levels of abnormally high glucose (hyperglycemia). Many patients, especially those with type 2 diabetes; also have elevated blood pressure (hypertension), chronic high levels of insulin (hyperinsulinemia) and unhealthy levels of

cholesterol and other blood fats (hyperlipidemia). All of these factors contribute to the long-term complications of diabetes, which include:

A) Vascular disease (diabetic angiopathy), atherosclerosis, heart conditions and stroke:

These cardiovascular disorders are the leading cause of death in people with diabetes.

B) Kidney disease (diabetic nephropathy):

Diabetes is the chief cause of end-stage renal disease, which requires treatment with dialysis or a kidney transplant.

C) Eye diseases:

These include diabetic retinopathy, glaucoma and cataracts.

D) Nerve damage (diabetic neuropathy):

This includes peripheral neuropathy, which often causes pain or numbness in the limbs, and autonomic neuropathy, which can impede digestion (gastroparesis) and contribute to sexual dysfunction and incontinence. Neuropathy may also impair hearing and other senses.

F) Impaired thinking:

Many studies have linked diabetes to increased risk of memory loss, dementia, Alzheimer's disease and other cognitive deficits.

G) Cancer:

Diabetes increases the risk of malignant tumors in the colon, pancreas, liver and several other organs.

H) Musculoskeletal disorders:

Conditions ranging from gout to osteoporosis to restless legs syndrome to myofascial pain syndrome are more common in diabetic patients than nondiabetics.

I) Pregnancy complications:

Diabetes increases the risk of preeclampsia, miscarriage, stillbirth and birth defects.

J) Diabetic ketoacidosis:

A lack of insulin can force the body to burn fats instead of glucose for energy. The result is a toxic byproduct called ketones, along with severe hyperglycemia (9).

►DM modern treatments and its limitation:

Patients who are diagnosed with diabetes usually require regular monitoring by various healthcare providers to manage their condition and reduce the risk of complications. Diet and exercise are crucial in managing diabetes. Some patients with metabolic forms of diabetes are able to control their disease using only these lifestyle interventions, which help the body use glucose (blood sugar) and prevent or reduce hyperglycemia. Some people with other forms of diabetes, including gestational diabetes, type 2 diabetes, secondary diabetes and maturity-onset diabetes of the young, also are prescribed insulin. Forms of insulin administration include syringe injections, insulin pumps, insulin pens and jet injectors and inhaled insulin. Many patients are prescribed antidiabetic agents.

Oral diabetes medications include:

1) Alpha-glycosidase inhibitors
2) Biguanides
3) Meglitinides
4) Sulfonylurea
5) Thiazolidinediones

In addition, patients may be prescribed a glucagon kit. Glucagon is a hormone that acts against insulin and can be injected in cases of severe hypoglycemia or insulin shock. Patients with diabetes are often prescribed other medications, including antihypertensive and cholesterol drugs, to treat related conditions. Patients who have or are at high risk for heart conditions may be advised to take low-dose aspirin daily.

People with diabetes need to perform glucose monitoring according to the schedule devised by their care team. Some patients use a glucose meter occasionally, but others, especially those using insulin or antidiabetic agents, must test several times a day. Patients at risk for diabetic ketoacidosis are advised to perform ketone tests. In addition to these self-tests, patients will have glycohemoglobin tests or fructosamine tests periodically performed by their physician to assess long-term control of glucose.

Limitation;-

1. Continuous blood glucose monitoring
2. Noninvasive monitoring
3. Improved diagnosis

4. Targeted molecular imaging
5. Understanding mechanisms Therapy problems
6. Improved insulin delivery
7. Islet cell transplantation
8. Oral insulin
9. Closed-loop insulin delivery (10).

►Herbal Medicine:

Literature has suggested the utilization of herbal medications for the treatment of insulin dependent and noninsulin dependent diabetes since time immemorial. Plants possessing antidiabetic properties may be suitable as adjunct to the existing therapies or as a prospective source of new hypoglycemic compounds. Since time immemorial, naturopathic therapies have been applied for a number of health ailments and continue to gain popularity in the present arena as well. Ancient literature revealed that diabetes was a known disease since Brahmic period and finds a mention in Ayurvedic literature, Sushruta samhita written in fourth and fifth centuries BC.

Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information reports about 800 plants that may possess anti-diabetic potential (11). The chemical structures of a phytomolecule play a critical role in its antidiabetic activity. Several plant species being a major source of terpenoids, flavonoids, phenolics and other bioactive constituents have shown reduction in blood glucose levels (12).

►Flavonoids:

Over 5000 different flavonoids have been isolated and identified from plant sources; these Compounds are extensively distributed in the plant kingdom, particularly in photosynthesizing plant cells (13, 14). Flavonoids are a diverse group of polyphenolic compounds primarily known as the pigments responsible for producing the many colors present in flowers, fruit and leaves. These polyphenolic compounds were well known for their medicinal properties in health long before they were more closely evaluated in studies.

Flavonoids are composed of a 15-carbon (C6–C3–C6) skeleton and two benzene rings joined by a linear 3-carbon chain. Flavonoids can be divided into multiple subgroups according to the substitution patterns of the ring C, and flavonoids within the same class can be differentiated by the substitution of A and B (15, 16). There are six major subgroups of flavonoids, including flavonols (including quercetin, kaempferol, and myricetin), flavanones (including eriodictyol, hesperetin, and naringenin), isoflavonoids (including daidzein, genistein, and glycitein), flavones (including apigenin and luteolin), flavans-3-ol (including catechin), and anthocyanins (including cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin).Instead that we are looking mostly three flavonoids such as quercetin, resveratrol (flavonols) catechin or epigallocatechin gallate(flavans-3-ol).

►Quercetin:

Its plant sources are apples, berries, red onions, cherries, broccoli, coriander, grapes, citrus fruits and tea etc (17).

Several studies have reported quercetin mechanism of action in diabetes, such as decreases in lipid peroxidation, increases in antioxidant enzymes (like SOD, GPX, and CAT) activities, inhibition of insulin dependent activation of PI3K, and reduction in intestinal glucose absorption by inhibiting GLUT2 (18, 19). Quercetin supplementation was therapeutic application and prevention of human disease augmented has been discovery of its activity like anti-cancer, cardio protective, anti inflammatory, anti viral, anti diabetic, anti oxidant and anti allergic (20).

►Resveratrol:

Resveratrol (3,5,40-trihydroxy-trans-stilbene), a redox active compound, is a phytoalexin found in a wide range of dietary sources, including grapes, wine (especially red wine) and peanuts.

Resveratrol shows mechanism of action in diabetes, such as improves resistance, ameliorates defective insulin signaling, prevents pancreatic beta cells apoptosis and dysfunctions, prevents abnormal glucose uptake and storage mitigates Hyperlipidaemia and dyslipidemia (21), it exhibits antioxidant, anti-inflammatory, cardioprotective, estrogenic and antitumor activities (22).

►Catechin or epigallocatechin gallate:

Epigallocatechin-3- gallate (EGCG) the most abundant catechin found in green tea has been shown to have several potential therapeutic properties like anti oxidant, anti inflammatory, anti-apoptotic and anti diabetic etc (23).

EGCG has been traditionally regarded as beneficial because of its antioxidant effects, which may aid in a number of clinical conditions such as cancer, obesity, atherosclerosis, diabetes and neurodegeneration. These age-related diseases are collectively characterized by increased production of reactive oxygen species (ROS) and/or insufficient cellular antioxidant capacity. Although balanced cellular ROS modulate a variety of physiological events including proliferation, differentiation, host defense and wound healing, they are highly reactive. Extensive ROS exposure causes deleterious damage of proteins, lipids and DNA, which leads to premature senescence and cell death (24).

EGCG has been shown to reduce neurotoxic proinflammatory cytokines in primary microglia, as well as suppressing the Aβ induced neuroinflammatory response of microglia, which is protective against indirect neurotoxicity. EGCG has also been shown in vitro and in vivo to shift amyloid precursor protein processing to the non-amyloidogenic a-secretase pathway through a protein kinase C-dependent process (25).

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

1. Quercetin;

Quercetin is a potent anti-inflammatory flavonoid, but its capacity to modulate insulin sensitivity in obese insulin resistant conditions is unknown. Cells and muscles were processed for analysis of glucose transporter 4 (GLUT4), TNFa and inducible nitric oxide synthase (iNOS) expression, and c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor-kB (NF-kB) kinase (IkK) phosphorylation. Quercetin treatment improved whole body insulin sensitivity by increasing GLUT4 expression and decreasing JNK phosphorylation, and TNFa and iNOS expression in skeletal muscle. Quercetin suppressed palmitate-induced up regulation of TNFa and iNOS and restored normal levels of GLUT4 in myotubes (26).

Monoamine oxidase-A (MAO-A) is the main enzyme in the metabolism of the neurotransmitter serotonin (5-hydroxytryptamine). Elevated activity of MAO-A in the brain may contribute to the pathogenesis of depressive disorders. Plant flavonoids, such as flavonol quercetin and flavone luteolin, have been suggested to be potential antidepressant compounds because they exert a suppressive effect on the MAO-A reaction (27).

Neuropathic pain is caused by lesion or disease of the nervous system, which results in abnormal spontaneous and evoked pain. The effect of quercetin (QUE) on neuropathic pain and the underlying mechanisms. QUE exerts anti-inflammatory effects and alleviates neuropathic pain through the inhibition of Toll-like receptor signaling pathway (28).

Quercetin is a well-known flavonoid, has low bioavailability. Quercetin nanoparticles (NQC) enhance its bioavailability. NQC were not explored for their potential therapeutic activities in Alzheimer's disease (AD). Hence, the present study was performed to evaluate the protective effect of NQC in comparison to free quercetin against scopolamine induced spatial memory impairments (29).

Quercetin, naringenin, and berberine are plant bioactives that can cross the blood-brain barrier and offer neuroprotection. The effect of them on expression of various glucose transporters and key components of brain insulin signaling, namely, insulin receptor substrate 1 (IRS 1), phosphatidyl inositol 3 kinase (PI3K), Akt 1 and low-density lipoprotein receptor-related protein 1 (LRP1) in brain of control, diabetic and bioactive-treated rats by Western blot. On the other hand, berberine and naringenin supplementation to diabetic animals

improved brain IRS 1 levels and restored GLUT 1 and GLUT 3 expression without significant effect on PI3K and Akt 1 activation and GLUT 4 levels (30).

2. Resveratrol;

Resveratrol (RSV) is a polyphenolic compound with potent antioxidant activity occurring in plants and various dietary products. Owing to its potent antioxidant activity and other biological activities, the compound has been evaluated for its ability to inhibit AR with the view that it may have a therapeutic role in diabetic complications (31).

Epigallocatechin-gallate (EGCG) and resveratrol (RSVL) are two of the most promising natural medicines. Their capacity to ameliorate cisplatin (CP)-induced disruption of renal glomerular filtration rate (GFR) in rats, and sought the mediatory involvement of lipid peroxidation (malondialdehyde [MDA]-level) and inflammatory cytokine (TNF-α). At the molecular level, CP triggers a high level of oxidative stress and systemic inflammation, events that were all abrogated with EGCG; better than RSVL or quercetin (32).

The development of diabetic nephropathy (DN) relays mainly on control of blood glucose and restrains hyperglycemic-induced oxidative stress. Oral treatment of diabetic rats with RSV alone or co-administered with RSU improved renal dysfunction indicated by a significant decrease in serum creatinine, urinary protein and urinary TGF-b1 when compared with diabetic control rats. Also, a significant increase in body weight, relative kidney weight with a significant decrease in serum glucose and glycated hemoglobin in diabetic treated groups when compared with diabetic control group. Hyperglycemic-induced oxidative stress in diabetic control rats indicated by a significant decrease in renal activities of catalase, superoxide dismutase, glutathione peroxidase and reduced glutathione level with a significant increase in malondialdehyde levels (33).

3. Epigallocatechin-gallate (EGCG);

The bioactivity of polyphenols is closely linked to their ability to interact with biological membranes. The in vitro effect of quercetin and epigallocatechin on the membrane anisotropy and transmembrane potential of peripheral blood mononuclear cells (PBMCs) The two tested polyphenols induced a dose-dependent hyperpolarizing effect and stiffening of the cell membranes for all tested subjects. Epigallocatechin gallate induced higher effects compared to quercetin on the membranes isolated from subjects with higher cardiovascular

risk. The decrease of membrane fluidity and the hyperpolarizing effect could explain the cardiovascular protective action of the tested compounds (34).

The effects of the major green tea polyphenol, (−)-epigallocatechin-3- gallate (EGCG), on high-fat–induced obesity, symptoms of the metabolic syndrome, and fatty liver in mice. EGCG treatment also decreased liver weight, liver triglycerides, and plasma alanine aminotransferase concentrations in high-fat–fed mice (35).

Quercetin, luteolin, and epigallocatechin gallate (EGCG) are flavonoids with a number of biochemical and cellular actions relevant to glucose homeostasis. Oral administration of quercetin, luteolin, and EGCG impaired glucose tolerance and blunted the effect of insulin to low blood glucose. Luteolin and EGCG, but not quercetin, inhibited glucose load-induced insulin receptor substrate-1(IRS-1) tyrosine and Akt phosphorylation in adipose tissue. Meanwhile, insulin-stimulated glucose uptake was also inhibited by these flavonoids (36).

Quercetin, luteolin, and epigallocatechin gallate enhanced glucose consumption with the positive regulation of AMP-activated kinase phosphorylation, and the AMP-activated kinase inhibitor compound C abolished their effects on glucose consumption. Luteolin and epigallocatechin gallate, but not quercetin, increased sirtuin 1 abundance, and their regulation of glucose consumption was also attenuated by co-treatment with sirtuin 1 inhibitor nicotinamide (37).

4. Objectives of Research/ Proposed Hypothesis:

1. The prime objective of the present work is to investigate the effect of combinations of some flavonoids on DM and its complications.
2. The other objective of determine the possible effect of flavonoids on pharmacokinetics parameter and bioavailability of modern antidiabetic agents.
3. Determine the effect of concurrent administration of flavonoids and modern antidiabetic drugs on DM and its complications.

5. Methodology to be adopted:

1. Procurement flavonoids
2. Dose selection, Preparation
3. Screening models
4. To study Pharmacokinetic parameter
5. To study Bioavailability parameter.

►Screening models:

Based on different mechanisms, following models were used in the present study.

1. Streptozotocin (STZ) induced diabetes:

Streptozotocin (STZ) is a naturally occurring chemical it particularly produces toxic to the beta cells of the pancreas. It is used in medical research as an animal model for hyperglycemia. STZ alters the blood insulin and glucose concentrations. Two hours after injection, the hyperglycemia is due to the decreased in blood insulin levels. Six hours later, hypoglycemia occurs due to the high levels of blood insulin. At last hyperglycemia develops and blood insulin levels drops. STZ impairs glucose oxidation and decreases insulin synthesis and release. It was observed that STZ at first abolished the B cell response to glucose (38).

2. **Alloxan induced diabetes:**

Alloxan is the next most commonly used chemical for induction of DM. It is a well-known diabetogenic agent widely used to induce Type 2 diabetes in animals. Alloxan is a urea derivative which causes selective necrosis of the pancreatic islet β-cells. It is used to produce experimental diabetes in animals such as rabbits, rats, mice and dogs. With this agent, it is possible to produce different grades of severity of the disease by varying the dose of alloxan used (39).

6. Importance of study/ Society application:

►International status:

Presently worldwide are more prone to DM disorder due to life style, obesity, stress related factors, so there is need to find out more effective and safe potent flavonoids combination effects.

►National Status:

Related to above research topic, DM disorder which are to be scientifically evaluated by pharmacotherputically.

►Significance of the study:

Proposed research involves attempt to evaluate effenicent and safe drugs from naturally treat against DM disorder and also its complication.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

Sr. No.	**Expected target to be achieved**	**1-6 months**	**7-10 months**	**11-13 months**	**14-20 months**	**21- 28 months**	**29-36 Month**
01	Flavonoids	Literature survey					
02	Procurement	Procurement flavonoids					
03	Dose selection, Preparation	Combination flavonoids					
04	Screening methods	Screening Methods with Combination flavonoids					
05	Pharmacokinetic parameter	Pharmacokinetic parameter					
06	Bioavailability parameter.	Bioavailability parameter					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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